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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,137	02/17/2004	Tamara Minko	RU-0223	2173

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/780,137	MINKO ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-6 and 8-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6 and 8-14* is/are rejected.

7)☒ Claim(s) *15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to the Amendment

The Amendment filed on 08/08/2006 in response to the previous Non-Final Office Action (05/08/2006) is acknowledged and has been entered.

Claims 4-6 and 8-15 are currently pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 4-6 **remain** rejected and **new** claims 8-10 and 13-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Trouet et al. (WO 01/91798, 2001).

Trouet et al. teach a prodrug for treating cancer comprising a biologically active entity linked to a masking moiety via a linking moiety (abstract). With regards to the biologically active entity, the WO document teaches (page 60, claim 51 of the WO document) that the biologically active entity includes, but is not limited to, BH3 peptides and anticancer agents such as anthracyclines, doxorubicin and camptothecins. With regards to the linking group, Trouet et al. teach (page 2, lines 17-23) that the linking moieties are preferably peptides having the amino acid sequence of $(Leu)_y(Ala\text{-}Leu)_xAla\text{-}Leu$ and $(Leu)_y(Ala\text{-}Leu)_xAla\text{-}Phe$, where y is 0 or 1 and x is 1, 2, or 3. With regards to the masking moiety, the WO document teaches (page 5, lines 21-33, page 15, lines 16-35 and page 32, lines 14 +) that the masking moiety may have biological activity such that prodrug is a dual prodrug and further, comprise large molecular weight biologically inert molecules such as PEG or HPMA. Trout et al. further teach (page 6, lines 18-24) a method of treating cancer comprising administering the prodrug to an animal in an effective amount to shrink or eradicate the tumor. Furthermore, the WO document teaches (page 35, lines 24+) a method of making the prodrug comprising condensing the masking moiety and biological entity with the linking moiety. Although Trouet et al. does not specifically teach that the linking moiety is a scaffold, the claimed limitation is an inherent property of a linking moiety because the specification discusses (page 29, line 33 to page 30, line 1) that a scaffold is a peptide of 1 to 10 amino acid residues. Thus, the claimed drug delivery

composition appears to be the same as the prior art. Furthermore, while Trouet et al. does not specifically characterize the high molecular weight biologically inert polymer such as PEG or HPMA as a multifunctional carrier or a cell-surface targeting moieties or as being the same, the claimed functional limitation would be an inherent property because as the specification teaches (page 23, lines 8-32) high molecular weight water-soluble polymers have been shown to preferentially accumulate in solid tumors such that they may act as both the multifunctional carrier and cell surface targeting moiety. Lastly, even though Trouet et al. does not explicitly teach that BH3 peptide is a suppressor of antiapoptotic cellular defense, the claimed limitation would be an inherent characteristic of a BH3 peptide because the specification discusses (page 9, lines 17-25) that exemplary antiapoptotic cellular defense components include BH3 peptides. In this case, the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

In response to this rejection, Applicants assert that the Trouet reference does not disclose or suggest a composition comprising an anticancer agent; a polyethylene glycol polymer and at least one of a BH3 peptide and luteinizing hormone-releasing hormone (LHRH), wherein a BH3 peptide and LHRH are used as a means of achieving targeted delivery of the anticancer agent to cancer because Trouet et al. only appears to suggest using an anticancer agent or a BH3 peptide as the biologically active entity in claim 51. As described above, Applicants assert that, in the present invention, the BH3 peptide and LHRH are used to specifically target the PEG-carried anticancer agent to the cancer cell surface and/or intracellular antiapoptotic cellular defense pathways.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertion that Trouet only contemplates using BH3 as the biologically active entity in claim 51 and not as a means of achieving targeted delivery of the anticancer agent to cancer, the Examiners concedes that Trouet teaches using the BH3 peptide as a biologically active entity. However, the Examiner recognizes the features upon which applicant relies (i.e., targeting of the anticancer agent) are not recited in the rejected claim(s). Although the claims are interpreted in

light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As such, the dual prodrug comprising at least a BH3 peptide linked via a peptide to a second intracellularly active biologically active entity such as doxorubicin and further, comprising large molecular weight biologically inert molecules such as PEG taught by Trouet et al. anticipates the instant claims.

New Rejections Necessitated by Amendment:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4-6 and 8-12 rejected under 35 U.S.C. 103(a) as being unpatentable over Pechar et al. (Bioconjugate Chemistry 2000; 11: 131-139) in view of Chatzistamou et al. (Clinical Cancer Research 2000; 6: 4158-4165).

Pechar et al. teach the synthesis of a water soluble polymer drug carrier system based on the biodegradable poly (ethylene glycol) block copolymer (abstract). Specifically, the reference teaches that the copolymer consisting of PEG blocks were linked together via an oligopeptide chain, wherein a tetrapeptide spacer was used to attach the oligopeptide blocks to an anticancer agent, e.g., doxorubicin. Moreover, Pechar et al. teach a method of treating cancer comprising administering an effective amount of said water-soluble dug carrier to inhibits tumor growth (page 138, 2nd column, *In Vivo Evaluation of Anti-Cancer Activity*).

Pechar et al. do not explicitly teach that the complex drug delivery complex further comprises a luteinizing hormone-releasing hormone.

Chatzistamou et al. teach an effective treatment of metastatic MDA-MB-435 human estrogen breast carcinomas which utilizes LH-RH analogues as targeted carriers for chemotherapeutics agents such as doxorubicin (Title and Abstract). Specifically, the references

teaches that targeted chemotherapy is based on the concept of linking cytotoxic radicals to a carrier, which is able to recognize cancer cells, wherein selective accumulation of the chemotherapeutic agent can be achieved in the tumor while sparing the healthy tissues from exposure (page 4158, 2nd column, 2nd full paragraph). Moreover, Chatzistamou et al. teaches that the LH-RH analogues specifically target LH-RH receptors present on a variety of human tumors (page 4158, 2nd column, 3rd full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the reference so as to generate a drug delivery targeted complex. One would have been motivated to do so because Chatzistamou et al. teaches that the targeted chemotherapy is based on the concept that by linking cytotoxic radicals to a carrier, which is able to recognize cancer cells, a selective accumulation of the chemotherapeutic agent can be achieved in the tumor while sparing the healthy tissues from exposure. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by adding a LHRH analog to the complex taught by Pechar et al. in view of Chatzistamou et al., one would achieve a drug delivery complex which specifically targets tumors having LH-RH receptors and treating said tumors.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Conclusion

Chatzistamou et al. teach, as described above, an effective treatment of metastatic MDA-MB-435 human estrogen breast carcinomas which utilizes LH-RH analogues as targeted carriers for chemotherapeutics agents such as doxorubicin. Trouet et al. teach, as described above, a dual prodrug comprising at least a BH3 peptide linked via a peptide to a second intracellularly active biologically active entity such as doxorubicin and further, comprising large molecular weight biologically inert molecules such as PEG. However, Chatzistamou et al. and/or Trouet et al, do not teach or suggest, alone or in combination, a drug delivery complex for treating cancer comprising a complex conjugate of the following components: an anticancer agent; a poly(ethylene glycol) polymer; a BH3 peptide; and lutienizing hormone-releasing hormone (LH-RH). As such, claim 15 appears to be free of the prior art and is objected to for being dependent from a rejected independent claim.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Patent Examiner
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BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER